PTO/SB/33 Equivalent

PRE-APPEAL BRIEF REQUEST FOR REVIEW

In re Patent Application of: KAMINSKI, Joseph M. Application No. 10/521,936 Filed: February 7, 2006 For: TRANSPOSON-BASED VECTORS AND METHODS OF NUCLEIC ACID INTEGRATION Group Art Unit: 1633 Examiner: HILL, Kevin Kai Confirmation No.: 6143	CERTIFICATE OF FAX TRANSMISSION I hereby certify that this correspondence and all marked attachments are being transmitted via facsimile to the USPTO Central Fax No. (571) 273-8300 on the date shown below: January 6, 2010 Heather Armstrong

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant requests review of the legal and factual basis of the rejections in the Final Office Action mailed on July 6, 2009 in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reason(s) stated in the accompanying Remarks/Arguments that begin on the following page.

REASONS FOR THE REQUEST

Claims 1-6, 15, 18-20 and 23-26 are pending in the present application, from which Claims 2-4, 19 and 24-26 are withdrawn. A Final Office Action was mailed July 6, 2009 after Applicant filed a Request for Continued Examination, and Claims 1, 5, 6, 15, 18, 20 and 23 stand rejected under 35 U.S.C. §103. Applicant requests pre-appeal brief review of these rejections.

Claim Rejections Under 35 U.S.C. §103

The Examiner maintained the rejection of Claims 1, 5-6, 15, 18 and 20 under 35 U.S.C. §103(a) as allegedly unpatentable over Handler *et al.* (1998. *PNAS* 95:7520-7525, "Handler") in view of Kim *et al.* (U.S. Patent No. 6,479,616, "Kim"), Katz *et al.* (1996. Virology 217:178-190, "Katz"), Elledge *et al.* (U.S. Patent No. 6,828,093, "Elledge") and Grigliatti *et al.* (U.S. Patent Publication No. 2002-0116723, "Grigliatti"). The rejection of Claim 23 under U.S.C. §103(a) was also maintained as allegedly being unpatentable over Handler in view of Kim, Katz, Elledge and Grigliatti as applied to Claims 1, 5-6, 15, 18 and 20 and further in view of McFarlane (1996. *Transgenic Res* 5(3):171-177, "McFarlane").

(1) The Examiner's application of prior art that he previously determined to be a nonobvious variant of the elected species was legal error

The Examiner has maintained his reliance on a cited reference directed to integrases (Katz) to illustrate the alleged obviousness of claims directed to transposases. In order to accomplish this, the Examiner relies on Elledge, Coates *et al.* (2005. *Trends in Biotechnology* 23(8):407-419, "Coates") and the instant specification. In so doing, the Examiner has reversed his own previous determination that transposases, recombinases and integrases are ***not*** obvious variants of each other.

At the outset of prosecution in this case, the Examiner required a species election between transposases, integrases and recombinases "due to their mutually exclusive characteristics," holding that "the species are not obvious variant of each another based on the current record" and that "the prior art applicable to one species would not likely be applicable to another species."[1] Applicant understood this to be a final determination, and fully complied with

[1] *See* Office Action mailed December 12, 2007 ("Election Requirement") at 2-3; Applicants' Response filed April 20, 2009, pages 5-7.

the species election in good faith, neither traversing nor petitioning the requirement. Applicant reasonably understood that the Examiner had determined these to be "patentably distinct species" and would therefore not raise prior art directed to integrases and recombinases against claims directed to transposases. During substantive prosecution, however, the Examiner nonetheless reversed his determination in order to expand the universe of prior art available to establish obviousness. It was error to do so.

Applicant has failed to find any previous case in which the Board sustained an obviousness rejection that was based on art disclosing a nonelected species, following an *explicit* determination that the cited species and the elected species were non-obvious variants.[2] This is unsurprising: general principles of estoppel should apply, and the Examiner should not be able to reverse an express legal holding on which Applicant has detrimentally relied, merely in order to facilitate a strained obviousness rejection.

The Examiner attempts to justify his legal gymnastics on the grounds that his previous determination was "prior to search and examination of the claims."[3] This is immaterial. Applicant recognizes that the PTO must have some means for controlling its administrative matters, and that election of species requirements are one mechanism for doing this. But, as the Examiner himself noted, Applicant's compliance with the requirement relieved him of an "examination and search burden."[4] The Examiner has materially benefitted from Applicant's compliance with the requirement, and the Examiner should not now be allowed to change his mind, and thereby avoid the consequences of his own determination. Applicant is bound by it; the Examiner should be as well.

(2) The facts adduced are insufficient to support a prima facie case of obviousness

In the outstanding Final Office Action, the Examiner asserts that "at the time of the invention, piggyBac transposase was an art-recognized species within the genus of **site-specific recombination enzymes** comprising transposases, integrases and recombinases."[5] This is

[2] In *Ex parte Capps*, No. 2008-001800 (May 29, 2009), for example, the obviousness rejection was based on a reference disclosing the elected species, and thus the Board's statement relating to effect of a species requirement on applicable prior art is merely dicta with respect to the issue presented in this appeal.

[3] *See* Final Office Action at 5.

[4] *See* Election Requirement at 3.

[5] Final Office Action, page 5, lines 22-24.

distinct from the assertion that the Examiner made in the Final Office Action dated December 18, 2008, in which the Examiner stated that "[n]either Handler et al, Kim et al nor Katz et al teach that the genus of integrases and recombinases embraces transposases" and relied on the disclosure of Elledge, a U.S. patent, to teach that **site-specific recombinases** include recombinases, transposases and integrases. This distinction is important: the Examiner relied on the disclosure of Elledge, which defines **site-specific recombinases** (not site-specific recombination enzymes generally) to assert that art directed to recombinases and integrases could be used in an obviousness rejection for claims directed to piggyBac transposase. Thus, the reliance on Elledge for obviousness no longer appears proper in view of the Examiner's current arguments.

In addition, as discussed in Applicant's response filed April 20, 2009, Elledge incorrectly defines the term "site-specific recombinase."[6] At best, Elledge was acting as his own lexicographer in defining this term for the purposes of describing the claimed invention. However, this is not a reflection of what the Examiner himself correctly described as generally understood in the art, namely, that these enzymes are not interchangeable or obvious variants of each other.

Coates states that "[v]iral integrases, transposases and site-specific recombinases mediate the integration of virus genomes, transposons or bacteriophages into host genomes."[7] Coates then goes on to describe each system ("Viral DNA integration systems," "Transposon-based DNA integration systems," "Recombinase-based DNA integration systems") under separate headings. Thus, contrary to Elledge's definition and the Examiner's assertion, it is clear from Coates that "site-specific recombinases" are distinct from viral integrases and transposases and do not encompass them. In addition, when read in its entirety, it is clear from Coates that a person of ordinary skill in the art would consider transposases, recombinases and integrases to be distinctly different in both evolutionary and mechanistic terms. The Examiner asserts that the same functional result is achieved, namely site-specific integration. However, the Examiner fails

[6] *See* Elledge, Col. 17, lines 16-19 ("The term 'site-specific recombinase' refers to enzymes that recognize short DNA sequences that become the crossover regions during the recombination event and includes recombinases, transposases and integrases.")
[7] *See* Coates, page 407, second column, first full paragraph.

to take into account that the different mechanisms and specificity of integration among transposases, recombinases and integrases would not make it obvious to the skilled artisan to substitute one type of enzyme for another, or to apply the teachings of one type of enzyme to either of the other types.

Applicant's own application simply teaches that "[i]ntegrating enzymes can be any enzyme with integrating capabilities." (*See* page 9, paragraph 51). This disclosure does not, as the Examiner appears to believe, support the view that transposases and integrases are obvious variants of one another.

Accordingly, even on the factual record provided by the Examiner, no legal conclusion of obviousness is justified.

(2) Even if the Examiner has established a prima facie case, Applicants have rebutted it

Applicant's description of each of Handler, Kim, Katz, Elledge and Grigliatti as described in Applicant's response filed April 20, 2009, was intended to illustrate the impropriety of combining these references and the fact that the combination does not teach or suggest the claimed subject matter. The claims relate to a composition containing a single nucleic acid construct that includes (i) a transgene, flanked by piggyBac transposon-derived terminal repeats, to be integrated into a target host genome for non-transient expression in the host, and (ii) a nucleic acid sequence that encodes a chimeric integrating enzyme that catalyzes integration of the transgene into the target host genome. The chimeric integrating enzyme, which refers to a genetically engineered recombinant protein wherein the domains thereof are derived from heterologous coding regions, includes a zinc-finger-derived DNA binding domain as well as an enzymatic integrating domain derived from piggyBac transposase.

Handler is directed to a two-vector system, wherein a first vector encodes a transgene (the medfly *w* gene) and a second vector encoding the normally regulated piggyBac transposase. Kim is primarily directed to chimeric zinc-finger proteins, which may include a regulatory domain, such as, for example an integrase or recombinase. Katz teaches a construct in which the DNA-binding domain of LexA repressor protein is fused to the catalytic domain of avian sarcoma virus (ASV) integrase enzyme. Elledge defines the term "site-specific recombinase" to refer to enzymes that include recombinases, transposases and integrases. Grigliatti references piggyBac

transposase in regard to the creation of inducible transposase producing cell lines, which is performed by creating transposase constructs in which a transposase gene is inserted downstream of a promoter and transformed into cell lines. As discussed above, Applicant believes that the art directed to integrases and recombinases (Kim, Katz) is not applicable to piggyBac transposase in view of the species election. Elledge has already been addressed in terms of its incorrect definition of "site-specific recombinase." The remaining combination of references, Handler and Grigliatti, do not teach or suggest the claimed subject matter of a single nucleic acid construct containing a transgene flanked by piggyBac transposon-derived terminal repeats and a region that encodes a chimeric integrating having a zinc-finger-derived DNA binding domain and an enzymatic integrating domain derived from piggyBac transposase. Accordingly, Applicant asserts that the claims are not obvious over the relevant combination of references.

Conclusion

Applicant respectfully requests review of the pending rejections. If, after review, the panel should find any remaining impediment to allowing one or more of the claims, Applicant respectfully requests that the panel decision specifically address any such remaining rejection(s) to permit Applicant to determine any necessary follow up actions.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 19-3140.

Respectfully submitted,

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